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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,488	02/16/2000	MAURICE MOLONEY	9369-98	6010

1059 7590 08/22/2008

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ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
08/22/2008	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MAURICE MOLONEY, JOENEL ALCANTARA, and GIJS VAN ROOIJEN

Appeal 2008-3488
Application 09/402,488
Technology Center 1600

Decided: August 22, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

The following claim is representative.

1. A method for the preparation of a recombinant polypeptide comprising

a) transforming a non-human host cell with an expression vector comprising:

(1) a nucleic acid sequence capable of regulating transcription in a host cell, operatively linked to

(2) a chimeric nucleic acid sequence that encodes a fusion protein, wherein said chimeric nucleic acid sequence comprises (a) a nucleic acid sequence encoding a full-length chymosin pro-peptide, linked in reading frame to (b) a nucleic acid sequence that is heterologous to the pro-peptide and that encodes the recombinant polypeptide, wherein the heterologous nucleic acid sequence is located immediately downstream of the nucleic acid sequence encoding the chymosin pro-peptide; operatively linked to

(3) a nucleic acid sequence encoding a termination region that is functional in said host cell,

b) growing the non-human host cell to produce said fusion protein,

c) obtaining said fusion protein from said non-human host cell, and

d) contacting said fusion protein with a mature form of an autocatalytically maturing aspartic protease that is capable of cleaving the chymosin pro-peptide, whereby said chymosin pro-peptide is cleaved from said fusion protein to release said recombinant polypeptide.

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Grounds of Rejection

1. Claims 1, 4-10, 12-16, 18-19, and 50-51 under 35 U.S.C. 112, first paragraph, for lack of enablement.

2. Claims 1, 4, 6-9, 13, 15, 19 and 51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh and Yonezawa.

3. Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh, Yonezawa and Fine.

4. Claims 14 and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh, Yonezawa and Dunn.

DISCUSSION

Background

"The present invention relates to … [a] method for recovering recombinantly produced polypeptides. The method involves expressing the recombinant polypeptide as a fusion protein with a pro-peptide. The pro-peptide-polypeptide fusion protein can be cleaved and the recombinant protein released under the appropriate conditions." (Spec. 1:3-7.)

1. Claims 1, 4-10, 12-16, 18-19, and 50-51 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

The Examiner finds that the Specification "does not reasonably provide enablement for practicing the claimed methods in any non-human host organism as encompassed by the claims, wherein cleavage of the fusion protein occurs under *in vivo* conditions in the host organism." (Ans. 8.) The Examiner further finds that the Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. (Ans. 18.)

Facts that should be considered in determining whether a specification is enabling include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of

the claims). *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Examiner discusses each of the *Wands* factors in the Answer. (Ans. 9.)

The Examiner acknowledges that "[a]t the time of the invention, methods for making transgenic animals and plants were known in the prior art," and the Examiner concludes that "in view of the analysis of the relevant Factors of *In re Wands* … that these methods were underdeveloped and highly unpredictable, the experimentation required to make the full scope of the claimed invention was *not* merely a considerable amount of routine experimentation, but required undue experimentation." (Ans. 18.) More particularly, the Examiner acknowledges that the issue of enablement with respect to the recombinant expression of the recited fusion protein in a bacterial, yeast or insect cell is not at issue. (Ans. 26.) The issue according to the Examiner is whether the Specification enables recombinant expression of the desired transgene to effect production of a fusion protein in a non-human host cell including a plant or non-human animal cell, and under *in vivo* conditions. (Ans. 26.)

Appellants contend that:

1. The breadth of the claims is commensurate with the Specification. (Br. 13.)

2. The state of the art and level of skill in the art of recombinant protein production was advanced as of the priority date. (Br. 14, 19.)

3. The level of predictability in the art is supplemented by the amount of guidance provided in the Specification. (Br. 19.)

4. The Specification includes working examples that further enable practice of the claimed methods. (Br. 20.)

5. There is no evidence that an undue quantity of experimentation would be required to practice the claimed methods. (Br. 21.)

With respect to plants and non-human animals, the Examiner finds that the state of the art regarding recombinant protein production in an animal or plant was neither "advanced" or "well within the capabilities of the skilled artisan" at the time of the invention as evidenced by Dyck, Sang, Mitalipov, Houdebine, Vain, Potrykus, Ristevski, Montoliu, Smith, Cameron and Sigmund. (Ans. 27-28.)

Appellants rely on Aigner, Butler, Janne, Sawers, Duncker, Yeh, Smith, Hiatt II, Mason and Lyons as evidence of enablement. (Br. 15-19.)

We conclude that the preponderance of the evidence supports the Appellants' position, and the rejection is reversed.

The existence of a non-operational embodiment within the scope of a claim does not invalidate a patent. *Texas Instruments v. U.S. International Trade Commission*, 805 F.2d 1558, 1562 (Fed. Cir 1986). "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid... . [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1348-49 (Fed. Cir. 2001); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). Thus the issue distills as to whether the Examiner has established on the evidence of record that the claims contain too many inoperable embodiments to be enabled.

With respect to non-animal host cells, the Examiner admits that "there is no dispute that representative examples of recombinant transgenic protein production in rabbits, sheep, goats, cows, pigs, and mice were well known at the time of the invention." (Ans. 28.) "Also, there is no dispute that representative examples of recombinant transgenic protein production in plants was well-known at the time of the invention." (Ans. 30.) Recombinant expression of the recited fusion protein in a bacterial, yeast or insect cell is not at issue. (Ans. 26.)

The Examiner's evidence, Sang, states that transgenesis techniques in poultry species, such as chick, were highly underdeveloped and unpredictable (see, e.g., p. 1179). (Ans. 12.) Mitalipov, cited by the Examiner, states that "somatic cell cloning has not yet been accomplished in primates" (p. 1367, column 2, bottom). Houdebine, cited by the Examiner states that, even among those animals that have been used to successfully produce recombinant proteins in their milk, gene transfer remains a difficult task. (Ans. 12-13.)

Appellants' evidence and arguments in the Reply Brief, p. 2-7, establish that when the teachings of the prior art as a whole are considered, the art has developed strategies to overcome some of the technical issues resulting in lack of predictability in the art proffered as evidence by the Examiner.

We conclude that the Examiner has not established on the record before us that the number of inoperative combinations encompassed by the claims is significant, and forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, *EMI Group North*

America Inc. v. Cypress Semiconductor Corp., 268 F. 3d at 1348-49, especially in view of the number of embodiments which the Examiner has indicated are enabled within the scope of the pending claims.

We conclude that the preponderance of the evidence supports the Appellants' position, and the rejection of the claims for lack of enablement is reversed. *See*, *e.g.*, *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

2. Claims 1, 4, 6-9, 13, 15, 19 and 51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh and Yonezawa.

According to the Examiner,

> Ward teaches a nucleic acid encoding a fusion protein, wherein the nucleic acid encodes (from the 5'-end) a signal sequence, a secreted polypeptide, a cleavable linker, wherein the cleavable linker is a chymosin pro-sequence, and two or more desired polypeptides . . . Ward teaches that upon construction of the fusion nucleic acid, it is inserted into an expression vector comprising regulatory sequences that are functional in the host to be transformed, including transcriptional regulatory sequences and transcriptional start and stop sequences . . . Ward teaches the fusion protein is produced by transforming an appropriate host cell with the fusion expression vector and culturing the transformant . . . followed by cleavage of the fusion protein using, *e.g.,* an endoproteinase . . . Ward acknowledges that recombinant expression of chymosin was known in the art at the time of the invention (*e.g.,* column 1, lines 13-19 and lines 36-40).

(Ans. 20.)

The Examiner acknowledges that Ward does not expressly teach the use of an autocatalytically maturing aspartic protease, particularly chymosin, to cleave the chymosin pro-peptide cleavable linker sequence in the recombinantly produced fusion protein. (Ans. 20.) However, the examiner concludes that:

> At the time of the invention, one of ordinary skill in the art would have recognized that chymosin is an appropriate endoproteinase for cleaving a fusion protein with an N terminal chymosin pro-peptide sequence as evidenced by Walsh. According to Walsh, in the cleavage of a fusion protein, "[a] specific protease must be used to limit proteolysis to the linker site only, and this site must be designed so that the recognition sequence is accessible to the protease" (p. 235, column 2, middle).

Id.

The Examiner relies on Walsh as teaching that

> Phe-Met at positions 105 and 106, respectively, of the chymosin substrate K-casein is a specific chymosin cleavage site and chymosin is the most specific of the aspartyl proteases (p. 236, column 1, top). Walsh teaches expression of a fusion protein having a linker comprising a Phe-Met chymosin cleavage site (p. 236, column 2 to p. 237, Figures 1-2). Walsh teaches "specific" cleavage of the fusion protein at the Phe-Met site at pH 4 and pH 6.8 by addition of mature chymosin (pp. 236, column 1, top and p. 240, column 1 and Table 1).

(Ans. 20-21.)

Yonezawa teaches four synthetic, chromogenic substrates cleaved by chymosin. (Yonezawa, abstract.) The Examiner relies on Yonezawa as teaching that:

> [M]ature chymosin cleaves a peptide (substrate II) specifically at a Phe-Met site at the P1-P1' positions (see particularly p. 58,

> Table 1). While it is noted that the results of Yonezawa are obtained with short peptides, it is noted that Walsh teaches that their results are "[i]n agreement with observations of chymosin activity on model peptide substrates" (p. 241, left column, top).

(Ans. 21.)

> The Examiner concludes that:
>
> [I]t would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ward, Walsh, and Yonezawa for practicing the method for fusion protein preparation and cleavage of Ward using mature chymosin as the endoproteinase cleaving agent, optionally co-expressing chymosin with the fusion protein to effect *in vivo* cleavage in the expression host. One would have been motivated to use chymosin as the fusion protein-cleaving agent in the method of Ward because Walsh teaches that a Phe-Met site is the specific cleavage site of K-casein, chymosin is the most specific of all aspartyl proteases, and both Walsh and Yonezawa demonstrate that chymosin can cleave a Phe-Met site.

(Ans. 21.)

Thus, the Examiner essentially argues that there would have been an expectation of success that chymosin would cleave the Phe-Met bond between a chymosin pro-peptide and a heterologous peptide of a fusion protein in view of the cited prior art.

Appellants contend that:

> There is simply no teaching or motivation in the cited art of preparing a recombinant polypeptide of interest by producing a fusion protein comprising a chymosin pro-peptide and the polypeptide of interest, and using a mature aspartic protease to cleave the chymosin pro-peptide sequence from the fusion

> protein to release the recombinant polypeptide of interest, as claimed.

(Br. 30.)

Appellants put forth the Declaration of Dr. Moloney in support of their position. Appellants argue that the Moloney Declaration establishes that it was known in the art that chymosin does not cleave any and all Phe-Met junctions (Br. 29; Declaration ¶9) and that hydrolysis of the Phe-Met of κ-casein (Walsh) is dependent upon the composition and sequence of amino acid residues in an extended region of the primary structure, and that a minimum chain length of five amino acid residues is essential to bring about any cleavage of the Phe-Met bond. (Declaration ¶6-8.)

Appellants argue that:

> Dr. Moloney refers to Example 1 and Figure 1 of the application as filed, and explains how they demonstrate that the Phe-Met bond that is present in the GST-Pro-Hirudin fusion protein is not cleaved by chymosin. Instead, cleavage occurs between a Phe-Val bond in that fusion protein.
>
> Dr. Moloney explains with reference to Figure 2 that cleavage of the His-Pro-cGH fusion protein also does not occur at a Phe-Met bond, but rather at a Phe-Ser bond. Thus, the Moloney Declaration and the prior art and application data discussed therein demonstrate that chymosin does not cleave proteins at any and all Phe-Met bonds.

(Br. 29; Declaration ¶ 8.)

Appellants conclude that:

> One of ordinary skill in the art would not have had a reasonable basis for expecting that an aspartic protease would be capable of cleaving a chymosin pro-peptide from a fusion protein to release the recombinant polypeptide, and did not know, for example, whether the aspartic protease would cleave

> the recombinant polypeptide at undesired sites and/or would cleave off too many or too few amino acid residues around the junction between the pro-peptide and the recombinant polypeptide. Without an assurance of accurate cleavage, there was no motivation to have employed an aspartic protease as presently claimed.

(Br. 44.)

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. *See In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Given the evidence before us, we agree with Appellants that the Examiner has failed to establish a reasonable expectation of success that an aspartic protease such as chymosin would have been an appropriate endoproteinase for cleaving a chymosin pro-peptide from a fusion protein. (Br. 30.) Given the absence of a reasonable expectation that chymosin would function appropriately in Ward's process, we also agree with Appellants that the Examiner has not adequately explained why one of ordinary skill in the art viewing the

cited references would have been prompted to substitute chymosin for Ward's proteases.

In view of the above, the obviousness rejection is reversed.

3. Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh, Yonezawa and Fine.

4. Claims 14 and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ward, in view of Walsh, Yonezawa and Dunn.

We find that neither Fine nor Dunn remedies the deficiencies of Ward, Walsh, and Yonezawa discussed herein. These obviousness rejections are reversed.

SUMMARY

The enablement and obviousness rejections of the Examiner are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

REVERSED

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